

has been filed concurrently herewith. A marked-up copy of the amended claims can be found at Tab C. The Applicants request that the amendment be entered to simplify the issues for appeal. Furthermore, the Applicants request reconsideration of the final rejection. The Applicants respectfully submit that the application is in condition for allowance and in support thereof the Applicants submit the following remarks:

Rejections under 35 USC § 112, 2nd paragraph.

Claims 16, 19, 25, and 30 were rejected under 35 USC § 112, 2nd paragraph as allegedly being indefinite because the metes and bounds of "a variant thereof" are not defined. The Applicants respectfully submit that the terms "consensus sequence" and its "variants" are well-established in the art. Examples of such variants are illustrated in the Tables on pages 8-9 in the present specification. A genetic variant in an amino acid sequence is simply a sequence substantially similar to the consensus sequence but having one or more substitutions of different amino acids into the sequence. For example, in Table 1, page 9, the consensus sequence HIV1 Subtype D is shown as SEQ ID NO. 8 (in the attached amendment to the specification at Tab A). One variant of this consensus sequence is SEQ ID NO. 9, in which arginine has been substituted for lysine at amino acid position 526, and threonine has been substituted for isoleucine at position 532. Another variant is SEQ ID. NO. 10, in which asparagine has been substituted for isoleucine at position 532. However, these variants are only a few examples. Other variants are readily apparent and available to those skilled in the art. For example, a recent search on the Los Alamos Database for "subtype D, env sequences," and "subtype E, env sequences" produced the many variants identified at Tabs D and E, respectfully.

The Examiner's insistence that the Applicants claim only the specific sequences disclosed in the specification in order to fully define the "metes and bounds" of the term "variant" is an improper application of 35 USC § 112, 2nd paragraph. There is nothing in that section of the patent statute that requires an Applicant to claim only preferred or expressly disclosed embodiments. The Applicants respectfully submit that the term "variants" is clear and definite to those skilled in the art, and request that the rejection be withdrawn.

The Examiner also rejects claim 25 because it "fails to point out what is the precise sequence structure of epitope I and II of HIV-1 subtype O." The Applicants respectfully submit that the rejection is moot in view of the amendments to claim 25.

Rejections under 35 USC § 112, 1st paragraph

Claims 16, 17, 19, 23, 25, and 29-30 were rejected under 35 USC 112, 1st paragraph, because the specification allegedly does not enable one skilled in the art to make or use the invention commensurate in scope with the claims.

The Examiner maintains that the claims must be limited to precise sequences in order to overcome the enablement requirement. The Examiner states that the claims must point out the “the precise sequences of the epitopes from different subtypes of HIV group M that are used in combination with disclosed epitope II of HIV-1 subtype D and epitope I of HIV-1 subtype E.” However, the standard for enablement is not whether the claims are limited to only expressly disclosed or preferred embodiments. Rather, the standard is whether the disclosure is sufficient to enable one skilled in the art to practice a claimed invention throughout its scope without having to engage in undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In the present case, one skilled in the art could simply, and without undue experimentation, test whether a particular combination would be useful in an immunoassay method as claimed. The peptides sequences are relatively short and readily prepared, and the general immunoassay methodologies are well-known in the art and easily carried out. Accordingly, the Applicants respectfully submit that

Rejections under 35 USC § 103

Claims 16, 17, 19, 23, 25, 29, and 30 were rejected under 35 USC § 103 as being unpatentable over De Ley et al. (WO 93/18054) in view of Chamaret et al. (FR 2730493-A1). According to the Examiner, Chamaret discloses the use of an antigen of HIV-1 group M, sub-type D (corresponding to what was previously SEQ ID NO. 6, now SEQ ID NO. 34.). The Examiner has also stated that De Leys teaches a peptide according to SEQ ID NO. 31 (formerly SEQ ID. NO. 3), which is also HIV-1 group M, sub-type D. The Examiner concludes that the claimed invention would have been obvious from the recited references.


The immunoassay method of the present invention involves combinations of certain antigens. One possible combination recited in claim 16 involves a mixture of an antigen from HIV-1, M-group, subtype D, and an antigen from a “different HIV1 subtype of the M group.” Thus, the second antigen according to claim 16 must be from a subtype other than subtype D. In contrast, in the combination the Examiner has suggested, both antigens are subtype D. The Examiner has not

provided any explanation as to how the combination of references, each teaching an antigen from subtype D, leads to a mixture in which one of the antigens is *not* from subtype D. Accordingly, the Examiner has failed to make a *prima case* of obviousness, and Applicants request that the rejection be withdrawn.

CONCLUSION

The Applicants respectfully submit that the application is now in condition for allowance. Should the Examiner feel a discussion would expedite the prosecution of this application, the Examiner is kindly invited to contact the undersigned.

Respectfully submitted,


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MARKED-UP VERSION WITH CHANGES SHOWN

17. (twice amended) The method of claim 16 wherein said antigen of an HIV-1-subtype D isolate corresponds to a sequence selected from the group consisting of SEQ ID NOs. [1] 29 to [11] 39.

23. (twice amended) The antigen mixture of claim 19 wherein said antigen of an HIV1-subtype D isolate corresponds to a sequence selected from the group consisting of SEQ ID NOs. [1] 29 to [11] 39.

25. (twice amended) The antigen mixture of claim 19, further comprising an antigen from epitope region I, amino acids 570-584, or epitope region II, amino acids 581-596, of HIV1-subtype O.

29. (twice amended) An immunoassay method for detection of an antibody against HIV comprising:

- a. providing a sample suspected of containing an antibody against HIV,
- b. contacting said sample with an antigen comprising a sequence selected from the group consisting of SEQ ID NOs. [1] 29 to [11] 39, said sequence having a minimum length of 7 amino acids, characterized in that said antigen is bound to a label which generates a detectable signal when the antigen is bound to said antibody, and
- c. detecting the signal generated as a measure of said HIV antibody in the sample.

HIV 1 Subtype E (CRF_001_AE) gp41 Epitopic Regions I and II Sequence Comparison:

Results found in Los Alamos Database; search criteria: "Subtype E, env Sequences":

Accession	Name	Subty pe	Count ry	Sampling Year	Genomic Region	Sequence Length	Organi sm
<u>AB032740</u>	95TH022	01_AE	TH	1995	Complete genome	9427	HIV-1
	95TNIH022						
<u>AB032741</u>	95TH047	01_AE	TH	1995	Complete genome	9430	HIV-1
	95TNIH047						
<u>AB052995</u>	93JPNH1	01_AE	JP		complete genome	9720	HIV-1
	AB052995						
<u>AF015916</u>	A01021.A8-1	01_AE	TH	1994	env gp160	2589	HIV-1
<u>AF015917</u>	A01021.A8-2	01_AE	TH	1994	env gp160	2589	HIV-1
<u>AF015918</u>	A01021.A8-3	01_AE	TH	1994	env gp160	2586	HIV-1
<u>AF015919</u>	E11429.A3-1	01_AE	TH	1994	env gp160	2577	HIV-1
<u>AF015920</u>	E11429.A3-2	01_AE	TH	1994	env	2577	HIV-1
<u>AF015921</u>	E11429.A3-3	01_AE	TH	1994	env gp-160	2577	HIV-1
<u>AF070703</u>	NI1144	01_AE	TH	1995	env	2589	HIV-1
<u>AF070704</u>	NI1145	01_AE	TH	1995	env	2586	HIV-1
<u>AF070705</u>	NI1146	01_AE	TH	1995	env	2553	HIV-1
<u>AF070706</u>	NI1147	01_AE	TH		env	1934	HIV-1
<u>AF070707</u>	NI1149	01_AE	TH	1995	env	2561	HIV-1
<u>AF070708</u>	NI1150	01_AE	TH	1995	env	2562	HIV-1
<u>AF070709</u>	NI1152	01_AE	TH	1995	env	2571	HIV-1
<u>AF070710</u>	NI1154	01_AE	TH	1996	env	2571	HIV-1
<u>AF070711</u>	NI1155	01_AE	TH	1996	env	2568	HIV-1
<u>AF070712</u>	NI1156	01_AE	TH	1996	env	2574	HIV-1
<u>AF070713</u>	NI1157	01_AE	TH	1996	env	2550	HIV-1
<u>AF164485</u>	93TH9021	01_AE	TH	1993	complete genome	9738	HIV-1
<u>AF197338</u>	93TH057	01_AE	TH	1993	complete genome	9645	HIV-1
<u>AF197339</u>	93TH065	01_AE	TH	1993	complete genome	9612	HIV-1
<u>AF197340</u>	90CF11697						
	AF197340	01_AE	CF	1990	complete genome	9628	HIV-1
<u>AF197341</u>	90CF4071						
	AF197341	01_AE	CF	1990	complete genome	9597	HIV-1
<u>AF219267</u>	FIN92168						
	AF219267	01_AE	FI		vpu, env, nef	3084	HIV-1
<u>AF219268</u>	FIN9257						
	AF219268	01_AE	FI		vpu, env, nef	3090	HIV-1
<u>AF219273</u>	FIN9379						
	AF219273	01_AE	FI		vpu, env, nef	3078	HIV-1
<u>AF259954</u>	CM235-2	01_AE	TH	1990	complete genome	9734	HIV-1
<u>AF259955</u>	CM235-4	01_AE	TH	1990	complete genome	9734	HIV-1
<u>AF321083</u>	EFRA	01_AE	FR		env	2568	HIV-1
<u>AJ277818</u>	CA10 HIM277818	01_AE	CM		env, gp160	2610	HIV-1
<u>AY008714</u>	97CNGX2F						
	97CNGX-2F	01_AE	CN	1997	complete genome	8859	HIV-1
<u>AY008718</u>	97CNGX11F						
		01_AE	CN	1997	complete genome	8806	HIV-1
<u>L14572</u>	CM240X	01_AE	TH		env v3 tat nef rev	3199	HIV-1
<u>U08456</u>	93TH966.8	01_AE	TH	1993	vpu		
<u>U08457</u>	93TH975.15	01_AE	TH	1993	env	2836	HIV-1
<u>U08458</u>	93TH976.17	01_AE	TH	1993	env	2830	HIV-1
<u>U09131</u>	92TH022.4	01_AE	TH	1992	env	2833	HIV-1
<u>U39255</u>	TH921104	01_AE	TH	1992	env	2830	HIV-1
<u>U39256</u>	TH920142				env	2586	HIV-1
	92TH001.42	01_AE	TH	1992	env	2556	HIV-1
<u>U39260</u>	TH920149	01_AE	TH	1992	env	2556	HIV-1
<u>U39261</u>	TH921110	01_AE	TH	1992	env	2586	HIV-1
<u>U48264</u>	KH03	01_AE	TH	1993	env	2577	HIV-1
<u>U48266</u>	KH08	01_AE	TH	1993	env	2604	HIV-1
<u>U51188</u>	90CF402 90CR402						
	CAR-E 4002	01_AE	CF	1990	complete genome	9843	HIV-1
<u>U51189</u>	93TH253	01_AE	TH	1993	complete genome	9720	HIV-1
<u>U54771</u>	CM240	01_AE	TH	1990	complete genome	9203	HIV-1

AA-Sequences found (Subtype E)

(= some strains missing for which no AA sequences of gp 41 could be found in database)

95TH022 95TNIH022	KQLQARVLAVERYLKDQKFLGLWGCSGKIVCTTAVPWNS
95TH047 95TNIH047	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
93JPNH1 AB052995	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
A01021.A8-1	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
A01021.A8-2	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
A01021.A8-3	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
E11429.A3-1	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
E11429.A3-2	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
E11429.A3-3	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
NI1144	KQLQARVLAVERYLKNQKFLGLWGCSGKIICTTAVPWNS
NI1145	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
NI1146	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
NI1147	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
NI1150	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
NI1152	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
NI1154	KQLQARVLAVERYLKDQKFLGLWGCSGKIICPTAVPWNS
NI1155	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
NI1156	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
NI1157	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
93TH9021	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
90CF11697 AF197340	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNT
FIN92168 AF219267	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
FIN9257 AF219268	KRLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
FIN9379 AF219273	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
CM235-2	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
CM235-4	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
EFRA	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
CA10 HIM277818	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
97CNGX2F 97CNGX-2F	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
97CNGX11F	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
93TH966.8	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
93TH975.15	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
93TH976.17	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
92TH022.4	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
TH921104	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
TH920142 92TH001.42	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNI
TH920149	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNN
TH921110	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
KH03	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
KH08	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
90CF402 90CR402	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
CAR-E 4002	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS
93TH253	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPStop
CM240	KQLQARVLAVERYLKDQKFLGLWGCSGKIICTTAVPWNS

HIV 1 Subtype D gp41 Epitopic Region I and II Sequence Comparison:

Results found in Los Alamos Database; search criteria: "Subtype D, env Sequences":

<u>Accession</u>	<u>Name</u>	<u>Subty pe</u>	<u>Coun try</u>	<u>Sampling Year</u>	<u>Genomic Region</u>	<u>Sequence Length</u>	<u>Orga nism</u>
<u>Blas AF13</u> <u>t 3821</u>	MB2059	D	KE		complete genome	10035	HIV-1
<u>Blas AF21</u> <u>t 9271</u>	FIN93167 AF219271	D	FI			3090	HIV-1
<u>Blas AF21</u> <u>t 9272</u>	FIN93178 AF219272	D	FI			3026	HIV-1
<u>Blas AJ277</u> <u>t 820</u>	CI13 HIM277820	D	CI		env, gp160	2526	HIV-1
<u>Blas AJ320</u> <u>t 484</u>	HIM320484	D	UG	1992	complete genome	9745	HIV-1
<u>Blas AJ401</u> <u>t 037</u>	97DC.KCD4	D	CD	1997	env	2579	HIV-1
<u>Blas J0365</u> <u>t 3</u>	JY1 Z84	D	CD		vpu, env, tat, rev, nef	2653	HIV-1
<u>Blas K034</u> <u>t 54</u>	ELI	D	CD	1983	complete genome	9176	HIV-1
<u>Blas K034</u> <u>t 58</u>	Z6 Z2Z6 Z34	D	CD	1985	pol, vif, vpr, tat, rev, vpu, env, nef,	5159	HIV-1
<u>Blas L229</u> <u>t 45</u>	SE365A2	D	SN	1990	env TAT NEF VPU REV	3315	HIV-1
<u>Blas L229</u> <u>t 47</u>	UG266A2	D	UG	1990	env	3026	HIV-1
<u>Blas L229</u> <u>t 49</u>	UG269A	D	UG	1990	env, vpU, and nef genes, tat rev	3132	HIV-1
<u>Blas L229</u> <u>t 50</u>	UG274A2	D	UG	1990	env TAT NEF VPU REV	3288	HIV-1
<u>Blas M226</u> <u>t 39</u>	Z2Z6 Z2 CDC-Z34	D	CD	1985	complete genome	9081	HIV-1
<u>Blas M273</u> <u>t 23</u>	NDK	D	CD	1983	complete genome	9143	HIV-1
<u>Blas U088</u> <u>t 03</u>	92UG005	D	UG	1992	env	2020	HIV-1
<u>Blas U088</u> <u>t 05</u>	92UG024-D	D	UG	1992	env	2556	HIV-1
<u>Blas U273</u> <u>t 99</u>	92UG021.16	D	UG	1992	env	2806	HIV-1
<u>Blas U274</u> <u>t 19</u>	93ZR001.3 ZR0013 UGAMK3 UG-AMK-3	D	US	1993	env gp160 partial nef	2842	HIV-1
<u>Blas U368</u> <u>t 67</u>	C971-416	D	UG		env	2571	HIV-1
<u>Blas U368</u> <u>t 68</u>	C971-418	D	UG		env	2571	HIV-1
<u>Blas U368</u> <u>t 71</u>	C971-412	D	UG		env	2571	HIV-1
<u>Blas U368</u> <u>t 84</u>	WHO15-726	D	UG		env	2583	HIV-1
<u>Blas U368</u> <u>t 85</u>	WHO15-721	D	UG		env	2583	HIV-1
<u>Blas U368</u> <u>t 86</u>	WHO15-474	D	UG		env	2583	HIV-1
<u>Blas U368</u> <u>t 87</u>	WHO15-476	D	UG		env	2583	HIV-1
<u>Blas U433</u> <u>t 86</u>	92UG024.2	D	UG	1992	env	2552	HIV-1
<u>Blas U650</u> <u>t 75</u>	87TZ4622	D	TZ	1987	env	2583	HIV-1
<u>Blas U888</u> <u>t 22</u>	84ZR085	D	CD	1984	complete genome	8975	HIV-1
<u>Blas U888</u> <u>t 24</u>	94UG1141	D	UG	1994	complete genome	8952	HIV-1

AA-Sequences found (Subtype D)

(= some strains missing for which no AA sequences of gp 41 could be found in database)

ELI (Referenz)	KQLQARILAVERYLKDQQLLGIWGCSGKHICTTNVPWNSS
MB2059	KQLQARVLAVERYLKDQQLLGIWGCSGKHICTTNVPWNSS
FIN93178	KQLQARVLAVERYLKDQQLLGIWGCSGKHICTTTVPWNSS
CI13	KQLQARVLAVERYLKDQQLLGIWGCSGRHICTTTVPWNSS
92UG001	KQLQARILAVERYLQDQQLLGSWGCSGRHICTTTVPWNSS
D_97DC.KCD4	KQLQARILAVERYLKDQQLLGIWGCSGKHICTTTVPWNSS
JY1 Z-84	KQLQARVLAVESYLKDQQLLGIWGCSGKHICTTTVPWNSS
Z6 Z2Z6 Z34	KQLQARILAVERYLKDQQLLGIWGCSGKHICTTTVPWNSS
Z2Z6 Z2 CDC-Z34	KQLQARILAVERYLKDQQLLGIWGCSGKHICTTTVPWNSS
NDK	KQLQARVLAVERYLRDQQLLGIWGCSGRHICTTNVPWNSS
92UG005	KQLQARVLAVESYLKDQQLLGIWRCSGKHICTTNVPWNSS
92UG021.16	KQLQARVLAVESYLKDQQLLGIWGCSGKHICTTNVPWNSS
93ZR001.3 ZR0013 UGAMK3 UG-AMK-	KQLQARVLAVERYLQDQQLLGSWGCSGRHICTTNVPWNSS
C971-416	KQLQARILAVESYLKDQQLLGIWGCSGKHICTTTVPWNSS
C971-418	KQLQARILAVESYLKDQQLLGIWGCSGKHICTTTVPWNSS
C971-412	KQLQARILAVESYLKDQQLLGIWGCSGKHICTTTVPWNSS
WHO15-726	KQLQARILAVERYLQDQQLLGSWGCSGRHICTTTVPWNSS
WHO15-721	KQLQARILAVERYLQDQQLLGSWGCSGRHICTTTVPWNSS
WHO15-474	KQLQARILAVERYLQDQQLLGSWGCSGRHICTTTVPWNSS
WHO15-476	KQLQARILAVERYLQDQQLLGSWGCSGRHICTTTVPWNSS
92UG024.2	KQLQARVLAVESYLKDQQLLGVWGCSGRHICPTRVPWNSS
87TZ4622	KQLQARXPAVESYLKDQQLLGIWGCSGRHICTTTVPWNSS
84ZR085	KQLQARILAVERYLKDQQLLGIWGCSGKHICTTTVPWNSS
94UG1141	KQLQARILAVESYLKDQQLLGIWGCSGKHICTTNVPWNSS